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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

DEFENDANT'S STATEMENT OF DISPUTED FACTS IN OPPOSITION TO PLAINTIFF'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

Defendant, Vysis, Inc., respectfully submits the following statement of disputed material facts, together with supporting evidence, in support of its opposition to Plaintiff's Motion for Partial Summary Judgment.

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
1. United States Patent No. 5,750,338 (the '338 patent) consists of the specification, including drawings, and the claims. The '338 patent contains six independent claims (claims 1, 7, 19, 27, 28 and 34). Each of these claims is generally directed to a method of, or a kit for, amplifying and/or detecting a target polynucleotide (i.e., a nucleic acid), wherein the target is first isolated on a support.	Each of the '338 patent claims recites "amplifying" a target polynucleotide (or sample). The claims require at least the steps of target capture (e.g., binding a support to the target polynucleotide and substantially separating the support and bound target polynucleotide from the sample) and amplification. U.S. Patent No. 5,750,338, cols. 32-36.
2. Each of the claims contains a step of "amplifying" the target polynucleotide or sample. For example, claim 1 provides: 1. A method for amplifying a target polynucleotide contained in a sample comprising the steps of: (a) contacting the sample with a first support which binds to the target polynucleotide; (b) substantially separating the support and bound target polynucleotide from the sample; and (c) *amplifying* the target polynucleotide.	No dispute.
3. The '338 patent specification sets forth seven examples of the methods taught by the inventors. The first three examples refer only to methods of target capture alone, and do not refer to amplification. The last four examples refer to combining target capture and methods	No dispute.

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of amplification. Between the end of target capture examples and the start of the amplification examples, the inventors expressly set forth their teachings with respect to amplification methods. Referring to the target capture methods described in Examples 1 through 3, the inventors stated: The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by ***nonspecific*** *replication using standard enzymes* (polymerases and/or transcriptases).	
4. The '338 patent makes it clear that the reference to non-specific amplification methods was intentional and pointed out that one of the express benefits of their invention was that it permitted the use of non-specific enzymes and non-specific primers: Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ **non-specific** enzymes or primers. **Thus no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.**	The reference to non-specific amplification was to point out the particular benefits of the invention when using non-specific amplification. Thus, because of the preceding target capture step, either specific or non-specific amplification can be used. Persing Decl., ¶ 11.

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5. The '338 patent specification sets forth four examples of the amplification methods contemplated by the inventors (Examples 4-7). Consistent with the teaching of the patent that sequence-specific primers and specific enzymes are not necessary, each example suggests and describes amplification methods that use only non-specific primers and enzymes.	Each example does **not** suggest and describe **only** non-specific primers and enzymes. Example 5 discloses the use of a specific primer. Persing Decl., ¶ 13.
6. Example 4 illustrates "the use of RNA polymerase to amplify target DNA." It describes a method for amplifying the capture DNA by non-specific amplification using polymerases that lack transcriptional specificity.	No dispute.
7. Example 4 discloses only non-specific amplification:	No dispute.
8. Example 5 describes a non-specific amplification method in which the target DNA is replicated using random (*i.e.*, non-specific) primers and non-specific transcription of that DNA into RNA: In this example, both non-specific replication of target DNA and transcription of that DNA are used to amplify capture target DNA... . . Because the primers are *random*, some will, simple (sic) as a matter of statistics, bind to and cause	Each example does **not** suggest and describe **only** non-specific primers and enzymes. Example 5 discloses the use of a specific primer. Example 5 discloses that "[a]lternatively, the double stranded DNA can be formed by synthesis starting from capture probe a" Col. 31, lines 48-49 of '338 patent. In this instance, the capture probe acts as the primer. Since the capture probe binds

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of statistics, bind to and cause replication of sample sequences, no matter what those sequences are	specifically to the target DNA, the capture probe would be a specific primer to the target. This is an example of specific amplification because the primer, capture probe a, binds to a specific, unique DNA sequence in the target organism. Persing Decl., ¶ 13.
9. Example 5 discloses only non-specific amplification.	For the reasons given above, Example 5 also discloses the use of a **specific** primer. Persing Decl., ¶ 13.
10. Example 6 describes replication of target DNA using DNA polymerase and *random* hexamer oligonucleotides "to bring about *non-specific* double-stranded DNA synthesis" using a series of repeated heat denaturation and enzyme replacement steps	No dispute.
11. Example 6 discloses only *non-specific* amplification.	No dispute.
12. Example 7 describes *non-specific* amplification using an RNA polymerase, Qß replicase: In this example, rRNA and RNA transcribed from target DNA is purified using a capture probe, described above. The hybrid duplex is then denatured and single stranded nucleic acids are then replicated *non-specifically* using Qß replicase…	No dispute.

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13. Example 7 discloses only nonspecific amplification.	No dispute.
14. The first pages of the '338 patent provide drawings of various methods encompassed by the invention.	No dispute.
15. The first 3 drawings (Figure 1a to Figure 3) depict target capture methods alone, without amplification.	No dispute.
16. Figures 4, 5 and 6 depict target capture followed by amplification using only non-specific primers or enzymes.	As mentioned, in Example 5, if the double stranded DNA is formed by synthesis starting from capture probe a, this would be use of a specific primer. Persing Decl., ¶ 13.
17. The drawings included in the patent are discussed and described in the text of the patent specification	No dispute.
18. The text of the specification expressly states that in each of the drawings that include amplification (Figures, 4, 5 and 6) "the isolated target is *non-specifically* amplified to form a multitude of amplification products."	As mentioned, in Example 5, if the double stranded DNA is formed by synthesis starting from capture probe a, this would be use of a specific primer. Persing Decl., ¶ 13.
19. One of ordinary skill in the art would have understood the term "amplifying" in the '338 patent to include only the non-specific amplification methods taught by the patent.	Those of ordinary skill in the art as of December 21, 1987 reading the specification of the '338 patent would not have understood the term "amplifying" in the claims of the '338 patent to be limited to non-specific types of

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	amplification. Persing Decl., ¶ 7.
20. One of ordinary skill in the art would not have understood the term "amplifying" to include other amplification methods that use sequence-specific primers or enzymes.	Those of ordinary skill in the would have understood that the term "amplify" in the claims includes specific amplification. Persing Decl., ¶¶ 7, 19.
21. The PCR method was first described at a scientific meeting in the summer of 1985 and was published in December 20, 1985.	No dispute.
22. Within the scientific community, PCR was immediately "big news."	No dispute.
23. The patent was meant to cover *new* amplification methods using non-specific primers, not already-known methods such as PCR.	Inventor Lawrie believed that the invention of the '338 patent was not limited to nonspecific amplification. Lawrie Depo., at 262, lns. 8-14, Ex. H to Banks Decl.
24. On December 15, 1989, Dr. James C. Richards, the Director of Business Development and Licensing for Gene-Trak Systems, admitted that the '338 patent encompassed only amplification with non-specific primers and explicitly contrasted the methods of the patent with other methods of amplification using specific primers. Dr. Richards' analysis was set forth in a letter to	Richards said in a document that the "338 patent application claimed non-specific primers or promoters but admitted at his deposition that at the time he wrote the document, he had not read the '338 patent application. Richards Depo, at 184, lns. 7-9, Ex. I to Banks Decl.

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one of Gene-Trak's partners, Amoco Technology Company.	
25. Dr. Richards first discussed the fact that the pending patent application encompassed the use of random, non-specific primers. He then discussed the effect of combining non-specific amplification with the use of an initial target capture step. Finally, he pointedly contrasted the invented method with other known methods that used specific primers or promoters (e.g., enzymes): Cetus, Sibia/Salk, Biotechnica, etc. all claim **specific** primers for amplification whereas the present invention claims uses of the opposite, namely, **non-specific** primer or promoters.... Following extensive washing, captured target polynucleotides could be released and the non-specific amplification process could take place.	Richards said in a document that the "338 patent application claimed non-specific primers or promoters but admitted at his deposition that at the time he wrote the document, he had not read the '338 patent application. Richards Depo, at 184, lns. 7-9, Ex. I to Banks Decl.
26. Gen-Probe's HIV-1/HCV Assay use a target-specific amplification technology called Transcription-Mediated Amplification (TMA).	No dispute.
27. TMA uses *specific* primers, *specific* promoters, and a *specific* polymerase enzyme that recognizes only those promoters.	No dispute.

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28. Gen-Probe's product does not use non-specific amplification.	No dispute.

Date: May 25, 2001

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